Annals of Carcinogenesis

Open Access

Austin Publishing Group

Editorial

A Perspective on Natural Products in Breast Cancer Carcinogenesis and Chemoprevention

Nagle DG*
Department of Biomolecular Sciences and Research Institute of Pharmaceutical Sciences, University of Mississippi, USA

***Corresponding author:** Dale G Nagle, Department of Biomolecular Sciences, School of Pharmacy, University of Mississippi, University, Mississippi, USA

Received: June 06, 2016; **Accepted:** June 07, 2016; **Published:** June 08, 2016

Editorial

The term "natural product" generally refers to either relatively crude extracts or other preparations of plant materials or to low-molecular weight chemical entities isolated from plants, animals, and microorganisms. Purified natural products (e.g., Paclitaxel, Vincristine, Vinblastine, Doxorubicin) have traditionally served as both a major source of new cancer chemotherapeutic agents and as molecular probes of novel biochemical pathways that have led to the development of new semi synthetic and synthetic antitumor drugs (e.g., Everolimus, Ixabepilone, Capecitabine, Gemcitabine, Epirubicin, Docetaxel) [1,2]. Moreover, both crude natural product preparations and pure natural compounds have recently emerged as new potentially cancer 'Chemopreventive' agents that are believed to either inhibit or reverse the process of breast cancer carcinogenesis [3]. Such substances range from simple antioxidants that nonspecifically suppress the mutagenic and genotoxic impact of Reactive Oxygen Species (ROS), to agents that selectively inhibit the cellular signaling pathways that contribute to the molecular basis of Tumorigenesis [2]. A variety of both structurally and mechanistically diverse natural products have been reported to exhibit breast cancer Chemopreventive activity. Curcumin from turmeric *Curcuma longa Linn*, Sauchinone from *Saururus chinensis*, Genipin from *Gardenia jasminoides* Ellis, lycopene from tomatoes, capsaicin from hot peppers, and a number of other plant-derived natural products have all been reported to inhibit molecular signaling mechanisms that are associated with the process of carcinogenesis, tumor growth, or metastasis [3].

Breast cancer chemoprevention

Currently, the only drugs that are approved by the U.S. Food and Drug Administration (FDA) to prevent breast cancer are anti-estrogens such as tamoxifen and raloxidene that suppress the emergence and growth of Estrogen-Positive (ER^+) forms of breast cancer [1]. A wide variety of agents have been reported to inhibit or reverse carcinogenesis, both *in vitro* and *in vivo* [2]. Studies have demonstrated that it is possible to block the process of carcinogenesis in animal models that have been induced to form tumors [2]. While many clinical studies are still currently underway [1], aside from anti-estrogens, few of these agents exhibit cancer Chemopreventive activity in the clinic and some even may stimulate the growth of certain tumor or exhibit other detrimental effects to patients (reviewed in [4]). Potter postulated a number of reasons for the repeated clinical failure of Chemopreventive agents. For instance, just as tumors require a combined chemotherapeutic regimen to be effective and reduce the emergence of resistance, single-agent Chemopreventive therapies are equally likely to be less effective. Other factors, such as diet, exercise, etc. may confound the clinical studies. While tempting, giving high doses may not produce the same desired effects observed with lower concentrations/doses observed in preclinical studies. Finally, the issue of timing may be of overwhelming importance. For example, Potter also suggests that it seems unlikely that relatively short-term Chemopreventive therapies would be sufficient to prevent or reverse all of the carcinogenic factors that have combined over the lifetime of a patient to ultimately manifest as a malignancy. All of these factors, and others, unite to make the practical application of Chemopreventive therapies as complicated and as potentially challenging as effective cancer treatment.

Carcinogenesis, chemoprevention and bioassays

Many reasons have been speculated for the apparent clinical failure of numerous cancer Chemopreventive agents that first exhibited the potential to suppress carcinogenesis *in vitro* and *in vivo* [4]. Yet, we could learn much from the exhaustive efforts of those endeavors to discover drugs to treat cancer. Perhaps, the selection of the molecular/cellular targets for chemoprevention is as important to their potential clinical success as target selection is in the field of chemotherapeutic drug discovery. To discover mechanism-targeted cancer therapeutics, a variety of factors must be carefully considered in antitumor bioassay development. These include molecular target identification, target validation, selecting a measurable process for bioassay, data measurement, the importance of both solid positive and negative controls, appropriate statistical analysis, validation of the bioassays, exclusion of experimental artifacts, the process of 'active' agent selection, and the criteria for identifying and deselecting nuisance compounds that exhibit apparent activity due to off-target effects (reviewed in [5]). If all of these key drug discovery assay factors are not given the same level of attention in the field of Chemopreventive agent discovery, the overall clinical potential of the leads will be similarly diminished. The clinical failure of new anticancer agents is usually because they do not produce the desired effects on tumors or because they exhibit pronounced side effects and toxicities that limit their safe use on patients [6]. Moreover, pharmaceutical industry studies indicate that both reasons for the clinical failure of drugs can be traced back to the dependence of discovery efforts on inadequately validated molecular/therapeutic targets [6]. Likewise, potential Chemopreventive targets must first be established by subjecting them to the same rigorous animal and human validation criteria as anticancer drug targets. When a clinical failure occurs, we should go back to the beginning and ask, "Was the primary mechanism(s) associated with the Chemopreventive agent

Citation: Nagle DG. A Perspective on Natural Products in Breast Cancer Carcinogenesis and Chemoprevention. Ann Carcinog. 2016; 1(1): 1002.

activity ever clinically validated to inhibit/reverse carcinogenesis in a disease model that is therapeutically relevant to the bioassay systems that were used to identify and characterize the agent?"

Selectivity and nuisance compounds

It is imperative that the mechanism-induced and mechanism-independent off-target effects of potential Chemopreventive agents must be distinguished from more distinct and selective effects. When screening natural products and other small molecules, the concept of "nuisance" compounds emerges [5]. It becomes critical that compounds that can generate numerous 'off-target' effects be considered as potential nuisance compounds for deselection, rather than as exciting leads that will only fail in more rigorous and less forgiving clinical studies. Many flavonoids, phenolics, and metal chelators have the capacity to bind critical enzyme cofactors while some directly bind and inhibit a wide variety of proteins, thus generating a magnitude of potential "off-target" and unwanted clinically effects [5]. Natural product-based translation inhibitors block disease-related protein synthesis, but also block the synthesis of other essential proteins. Cytostatic and cytotoxic compounds often produce effects on non-malignant cells. Even at relatively low concentrations, agents that suppress cell proliferation trigger cellular stress response that can easily be misinterpreted as inhibiting tumor cell migration, the interruption of wound healing, or as suppressing the metastatic spread of cancer cells. This is also where we must make the subjective decision of how to distinguish the difference between potential therapeutic mechanisms observed with relatively high *in vitro* drug concentrations and the mechanisms associated with the potent and selective effects of compounds on more sensitive targets. For example, thousands of publications report the potential benefits of the green tea catechin (-)-Epigallocatechin-3-Gallate (EGCG). The vast majority of its effects on disease-related *in vitro* molecular targets and *in vivo* animal efficacy studies use non-physiologically relevant high concentrations (i.e., 10 – 1000 μM) (reviewed in [7]). This is in spite of the fact that physiologically relevant sub-micromolar EGCG concentrations selectively affect anticancer targets such as DNA methyltransferases, Bcl-2 signaling, and the regulation of angiogenesis by Vascular Endothelial Growth Factor (VEGF). Therefore, it seems almost predictable that the effects of a molecule like EGCG on targets that it only inhibits at very high micromolar to millimolar concentrations are unlikely to ever be confirmed clinically.

Natural products have played a major role in the discovery of new chemotherapeutic agents and they are among the most important types of substances that have been identified with the potential to inhibit or reverse carcinogenesis. As the field of cancer chemoprevention continues to grow and mature, it becomes vitally important to recognize that, perhaps, the biggest limitation on the clinical development of effective agents that prevent cancer is in the rigor of the science that we conduct and in the level of standards applied to their peer review and quality control prior to dissemination.

References

1. National Cancer Institute at the National Institutes of Health. Drugs Approved for Breast Cancer.
2. Cragg GM, Pezzuto JM. Natural Products as a Vital Source for the Discovery of Cancer Chemotherapeutic and Chemopreventive Agents. Medical Principals and Practice. 2016; 25: 1-19.
3. Ko EY, Moon A. Natural Products for Chemoprevention of Breast Cancer. Journal of Cancer Prevention. 2015; 20: 223-231.
4. Potter JD. The Failure of Cancer Chemoprevention. Carcinogenesis. 2014; 35: 974-982.
5. Nagle DG, Zhou Y-D, Fattorusso E, Gerwick WH, Taglialatela-Scafati O. Mechanism-based screening for cancer therapeutics with examples from the discovery of marine natural product-based HIF-1 Inhibitors. Chapter 5.7 in Handbook of Marine Natural Products. Springer. 2012; 1111–1144.
6. Smith C. Drug Target Validation: Hitting the Target. Nature. 2003; 422: 341, 343, 345.
7. Nagle DG, Ferreira D, Zhou YD. Molecules of Interest: Epigallocatechin-3-Gallate (EGCG): Chemical and Biomedical Perspectives. Phytochemistry. 2006; 67: 1849–1855.

Ann Carcinog - Volume 1 Issue 1 - 2016
Submit your Manuscript | www.austinpublishinggroup.com

Citation: Nagle DG. A Perspective on Natural Products in Breast Cancer Carcinogenesis and Chemoprevention. Ann Carcinog. 2016; 1(1): 1002.